REMARKS

Claims 1-17 and 19-22 are currently pending. In addition, claims 5-14 and 16-18 have been withdrawn from consideration and new claims 23-27 have been added. New claims 23-27 are supported by the specification and do not contain new matter.[1]

I. 35 U.S.C. 112, First Paragraph Rejection

Reconsideration is requested of the rejection of claims 1, 3-4, 15, and 19-22 under 35 U.S.C. 112, first paragraph, as not sufficiently enabled by the specification.

Claim 1 is directed toward a method for treating neoplasia in a mammal. The method comprises treating the mammal with radiation therapy and a matrix metalloproteinase inhibitor.

The standard for enablement is whether one of ordinary skill in the art could make or use the claimed invention from the disclosures in the application coupled with information known in the art without undue experimentation.[2] In this case, the specification coupled with information generally known in the art, fully enables a person of ordinary skill to carry out the method of claim 1 **without undue experimentation**. The specification details numerous embodiments of compounds that may be employed in the method of claim 1, such as thiol group-containing amide or peptidyl based metalloprotease inhibitors and hydroxamate group- containing metalloprotease inhibitors.[3] The specification also details over 200 examples of specific matrix metalloproteinase inhibitors.[4] In addition, the

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[1]Claim 23 is supported by specification at pages 8-9; claims 23-27 are supported by specification at pages 95-102.

[2]U.S. v. Teletronics, Inc., 8 USPQ2d 1217 (Fed. Cir. 1988).

[3]See pages 35-37 of the specification.

[4]See pages 37-69 and 72-87 of the specification.

specification incorporates by reference over 350 patent references, which describe various matrix metalloproteinase inhibitors and processes for their manufacture that may be utilized in the present invention.[5]

Moreover, radiation therapy as used in claim 1 refers to the use of electromagnetic or particulate radiation and is known in the art. In addition, the specification describes radiation dosages as well as dosage regimes for the treatment of non-small lung cancer, small lung cancer, breast cancer, bladder cancer, and head and neck cancers.[6] Further, the specification details 88 examples of specific types of neoplasia disorders and numerous examples[7] that illustrate the use of radiation therapy and a matrix metalloproteinase inhibitor to treat neoplasia disorders such as lung cancer, breast cancer, bladder cancer, and head and neck cancer.

The Office asserts "the specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention *commensurate in scope* with these claims."[8] In arriving at this conclusion, the Office relied on In re Wands.[9] In the Wands case, the claim at issue required using an antibody "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least $10^9 M^{-1}$."[10] The Federal Circuit discussed several of the relevant factors, and concluded that "undue experimentation would not be required to practice the

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[5] See pages 72-87 of the specification.

[6] See pages 91-102 of the specification.

[7] See pages 8-9 of the specification for examples of specific neoplasia disorders; and see examples on pages 95-102.

[8] Paper 122803 at page 4.

[9] In re Wands, 858, F.2d 731, 8 USPQ2d 1400 (Fed. Dir. 1988).

[10] *Id.*, at 8 USPQ2d p. 1402.

invention."[11] Contrary to the Office's assertion, however, Wands supports the conclusion that a claim, such as claim 1, directed toward the treatment of "neoplasia" is sufficiently enabled by the instant specification.

One factor considered in Wands was the "breadth of the claims." The Federal Circuit noted that of 143 candidate antibodies produced by Wands, his testing of just nine and proving the required activity of just four, not even considering countless others which Wands did not make, was sufficient to support claims of the following breadth: "wherein said antibody is a monoclonal high affinity IgM antibody having a binding affinity constant for said HBsAg determinants of at least 10^9M^{-1}."[12] This breadth, deemed acceptable, is much broader than a claim limited to those antibodies that Wands either produced or tested. Against this background, the breadth of claim 1 in terms of the use of "neoplasia," is reasonable in light of the 88 examples of specific types of neoplasia disorders identified in the specification and numerous examples that illustrate the use of radiation therapy and a matrix metalloproteinase inhibitor to treat lung cancer, breast cancer, bladder cancer, and head and neck cancer. Patent applicants are not required to show a specific example for every possible embodiment of the claimed invention, so long as the specification and the general knowledge of the art would enable one of ordinary skill in the art to make and use the invention.[13]

For the foregoing reasons, the Office has failed to establish that a claim directed toward treatment of "neoplasia" generically, such as claim 1, is not sufficiently enabled by the present specification. Moreover, for all the foregoing reasons, the Office has failed to establish that Applicant's

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[11] *Id.*, at 8 USPQ2d p. 1406.

[12] *Id.*, at 8 USPQ2d 1405.

[13] In re Borkowski, 164 U.S.P.Q. 642, 645 (CCPA 1970).

elected species, lung cancer, is not sufficiently enabled by the present specification.

Claims 3 and 4 recite all of the elements of claim 1 and further specify specific matrix metalloproteinase inhibitors to be used, and are likewise enabled for all of the reasons stated with respect to claim 1. Claims 15 and 19-22 depend from claims 1, 3 and 4 and are likewise enabled for all of the reasons detailed regarding claims 1, 3 and 4.

Moreover, since the Office acknowledges that the specification is enabling for specific neoplasia disorders detailed therein,[14] claim 2 and new claims 23-27, which are each directed toward specific types of neoplasia listed in the specification, are also enabled.

II. 35 U.S.C. 112, Second Paragraph Rejection

Reconsideration is requested of the rejection of claims 3, 15, and 19-22 under 35 U.S.C. 112, second paragraph. Claim 3 has been amended to cancel the phrase "subject" and replace it with "mammal" as suggested by the Office. Claims 19-22 have been amended to cancel the phrase "combination is" and replace it with "radiation therapy and a therapeutically effective amount of a matrix metalloproteinase inhibitor or pharmaceutically-acceptable salt of a matrix metalloproteinase inhibitor are". In view of these amendments, the rejection is moot and may properly be withdrawn.

III. 35 U.S.C. 103(a) Rejection

Reconsideration is requested of the rejection of claims 1-4, 15, and 19-22 under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,753,653 ('653 Patent), in view of U.S. Patent No. 5,348,887 ('887 Patent).

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[14] Paper 122803 at page 4.

Claim 1 is directed toward a method for treating neoplasia in a mammal. The method comprises treating the mammal with radiation therapy and a matrix metalloproteinase inhibitor.

A *prima facie* case of obviousness requires a showing that (1) the prior art reference(s) teaches or suggests all the claim limitations; (2) either the references themselves or the knowledge generally available to one of ordinary skill in the art contains a suggestion or motivation to modify the reference or to combine reference teachings; and (3) there is a reasonable expectation of success.[15] In this case, the Office has not established that claim 1 is prima facie obvious in view of the cited art.

The '653 patent discloses a class of heteroaryl compounds that are described as inhibitors of metalloproteinases. According to the '653 patent, the disclosed compounds may be employed to treat a number of pathological disease conditions mediated by connective tissue degradation, including "rheumatoid arthritis, osteoarthritis, periodontal disease, aberrant angiogenesis, tumor metastasis and invasion, tissue ulceration, bone disease, HIV-infection, and complications from diabetes."[16] But nowhere does the '653 patent disclose or suggest using the disclosed compounds in combination therapy, either generally or with radiation therapy for the treatment of neoplasia, as recited by claim 1.

The '887 patent discloses nucleic acid compounds and recombinant DNA cloning vectors that encode a cell surface glycoprotein commonly found in lung cancer cells.[17] In general, the '887 patent is directed toward the production of monoclonal antibodies specific for the glycoprotein. According to the '887 patent, the monoclonal antibodies may be used as an alternative method for diagnosis, prognosis, and therapy in lung cancer patients.[18] But nowhere does the '887 patent disclose or suggest using the monoclonal antibodies in combination

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[15] See MPEP § 2142.
[16] Id. at column 2, lines 7-15.
[17] U.S. Patent No. 5,348,887, column 1, lines 12-16.
[18] Id. at column 1, lines 18 - 55.

therapy, either generally or with radiation therapy for the treatment of neoplasia. More importantly, nowhere does the '887 patent disclose or suggest the use of a matrix metalloproteinase inhibitor in combination with radiation for the treatment of neoplasia as required by claim 1.

In the absence of any disclosure of the combination employed in claim 1, a *prima facie* case for obviousness is lacking.

According to the Office a skilled artisan would be motivated to combine the disclosure of the '653 patent with the disclosure of the '887 patent to arrive at the combination of claim 1 because the '653 patent is said to disclose a compound for inhibiting the activity of metalloproteinases and the '887 patent is said to disclose that the most effective forms of therapy for the treatment of lung cancer is "radiation therapy and surgery".[19] But the cited art, taken singly or together, provide no basis for this conclusion.

Among the many compounds and classes of compounds the '653 and the '887 patents propose, none offer any guidance that would have motivated a skilled artisan to prepare the combination employed in claim 1.

The '653 patent discloses a class of heteroaryl compounds that are described as inhibitors of metalloproteinases. The reference does not disclose or suggest the combination of these compounds with any other agent generally, let alone in combination with radiation therapy as employed in claim 1. And, while the '653 patent discloses that matrix metalloproteinase inhibitors may be used to treat diseases mediated by "connective tissue degradation" including "tumor metastasis and invasion," this disclosure is so vague and general to be non-informative.

The '887 patent discloses a monoclonal antibody that may be used for diagnosis, prognosis, and therapy in lung cancer patients. Of the 66 columns of disclosure in the '887 patent, the Office focuses on **one sentence** in the summary of invention that states radiation and surgery

[19] Id.

were effective forms of therapy for the treatment of lung cancer at the time the patent was filed. The very same paragraph of the '887 patent, however, states that the use of these methods results in "fewer than" a one-third survival rate beyond five years. The rest of the summary of invention in the '887 patent discloses the benefits of an immunological approach (i.e., monoclonal antibodies) for both the treatment and diagnosis of lung cancer. Nowhere else does the '887 patent disclose or suggest the use of radiation for the treatment of lung cancer. Viewed in its entirety, therefore, the disclosure of the '887 patent would actually have led a skilled artisan away from the combination of claim 1 as the '887 patent suggests the benefits of an immunological approach over either surgery or radiation for the treatment of lung cancer. The entire disclosure of a prior art reference must be considered and can provide sufficient teaching away to defeat an inference of obviousness.[20]

Even more revealing, not one of the cited references discloses or suggests combining a matrix metalloproteinase inhibitor and radiation therapy for use in the treatment of neoplasia, as recited in claim 1. Accordingly, a skilled artisan empowered with the cited art cannot fairly be deemed to be motivated to select a matrix metalloproteinase inhibitor disclosed in the '653 patent and combine it with the brief mention of the common therapy for lung cancer at that time in the summary of invention in the '887 patent to form a combination for use in treating neoplasia, as required by claim 1. As stated in MPEP 2143, where there is no motivation to modify a reference as proposed, the proposed modification is not obvious.

For the foregoing reasons, the Office has failed to establish that a claim directed toward a combination of a matrix metalloproteinase inhibitor and radiation therapy for use in the treatment of neoplasia, such as claim 1, is *prima facie* obvious in view of the '653 patent and the '887 patent. Claims 3 and 4 recite all of the elements of claim 1 and further specify

[20] See, e.g., Ex parte Thumm, 132 USPQ 66.

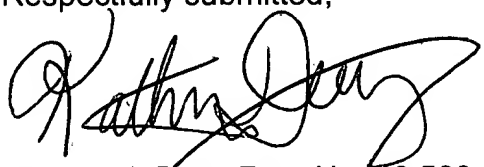
specific matrix metalloproteinase inhibitors to be used, and are likewise patentable over these references for the reasons stated with respect to claim 1 and by reason of the additional requirements they introduce. Claims 15 and 19-22 depend from claims 1, 3 and 4 and are likewise patentable over these references for the reasons stated with respect to claims 1, 3 and 4 and by reason of the additional requirements they introduce.

IV. Conclusion

In light of the foregoing, Applicants request entry of the claim amendments, withdrawal of the claim rejections, and solicit an allowance of the claims. The Examiner is invited to contact the undersigned attorney should any issues remain unresolved.

The applicants do not believe any fees are due as a result of filing this amendment, however, the Commissioner is hereby authorized to charge any underpayment and credit any overpayment of government fees to Deposit Account No. 19-1345.

Respectfully submitted,



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